DRUG DELIVERY—RECTAL ROUTE

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INTRODUCTION

Drug Delivery Routes

Although administration via the peroral route is the most commonly targeted goal of new drug and dosage form research and development, oral administration is not always feasible or desirable. The potential for oral dosage form development is severely limited for active agents that are poorly absorbed in the upper gastrointestinal (GI) tract and unstable to proteolytic enzymes. Some agents cause local stomach or upper GI irritation or require doses in excess of 500 mg. Certain patient populations, notably children, the elderly, and those with swallowing problems, are often difficult to treat with oral tablets and capsules. Additionally, treatment of some diseases is best achieved by direct administration near the affected area, particularly with diseases involving ophthalmic, otic, dermal, oral cavity, and anorectal tissues. Although oral administration can be used for drugs targeted for some of these diseased tissues, exposure of the entire body compartment to the administered drug is inefficient and can lead to undesired adverse effects. Rectal drug administration is amenable, however, to both local and systemic drug delivery. It has been effectively utilized to treat local diseases of the anorectal area as well as to deliver drugs systemically as an alternative to oral administration. In this article, factors influencing the utilization of rectal drug administration as well as the advantages and disadvantages of this approach, are discussed. A survey of the pharmaceutical literature for the last 5–7 years suggests that this administration route has not received a great deal of attention in the pharmaceutical community. Relatively few articles have appeared in the literature (1–4) and new products have not captured a significant segment of the pharmaceutical market. Although rectal drug administration is unlikely to ever become a commonly accepted route of administration, the utilization of this technology for particular applications and therapeutic problems offers an alternative delivery route which can be successfully applied in drug therapy.

Rectal Formulations Available

Solid suppositories

Solid suppositories are the most common dosage form used for rectal drug administration and represent greater than 98% of all rectal dosage forms. Typically, these are torpedo-shaped dosage forms composed of fatty bases (low-melting) or water-soluble bases (dissolving) which vary in weight from 1 g (children) to 2.5 g (adult). The composition is largely dictated by the physicochemical properties of the drug and the desired drug release profile. Lipophilic drugs are usually incorporated into water-soluble bases while hydrophilic drugs are formulated into the fatty base suppositories. Theoretically, this method maximizes removal of the drug from the suppository base to the immediate environment of the rectal cavity or lower colon. For suppositories made from fatty bases, melting should occur rapidly near body temperature (37°C). Ideally the resultant melt would readily flow to provide thin, broad coverage of the rectal tissue, thereby minimizing lag time effects due to slow release of the drug from the suppository base. Water-soluble suppositories should likewise readily dissolve at 37°C to facilitate drug release and subsequent absorption. With both fatty-base and water-soluble suppositories, the potential effects of incorporated drug on melting or dissolution properties need to be evaluated. Examples of fatty bases and water-soluble bases suitable for suppository formulations are shown in Table 1. Although not comprehensive, the list shows the variety of bases from which a formulator may choose.

Solutions

Solutions, suspensions, or retention enemas represent rectal dosage forms with very limited application, largely due to inconvenience of use and poor patient compliance. In many cases, these formulations are utilized to administer contrast media and imaging agents for lower GI roentgenography. Although drug absorption from solutions has been shown to exceed that from solid suppositories in some cases (5), this particular administration route is only

Table 1 Suppository bases

Vehicle	Melting range (°C)	Solidification point (°C)
Fatty bases		
Witepsol	32–44	27–38
Cocoa butter	30–35	24
Hard butters	36–45	32–40
Estarinum	29–50	26–40
Suppocire	35–45	30–37
Agrasup A;H	35–40	—
Water soluble		
Myrj 51	39–42	39
PEG[a]	38–49	38–42
Tween 61	35–49	—

[a]Polyethylene glycol.

(From *Modern Pharamaceutics;* Banker, G. S., Rhodes, C.T., Eds.; Marcel Dekker, Inc.: New York, Basel 1979.)

infrequently employed and will not be discussed here in detail. Recent studies utilizing liquid formulations that gel at body temperature are discussed in the Gels/foams/ointments section.

Gels/foams/ointments

The use of gels, foams or ointments for rectal administration can afford advantages over liquid formulations because retention of the dosage form in the rectal cavity reduces patient compliance problems. Drug release with semisolid dosage forms is usually limited to local indications such as hemorrhoids and lower bowel inflammation (proctitis). Drug release and subsequent pharmacologic action is usually faster with semisolid formulations than with solid suppositories since a lag time is not required for melting or dissolution.

Miyazaki et al. (1) investigated thermoreversible gels formed by a xyloglucan polysacharide derived from tamarind seed. Liquids containing 1–2% xyloglucan formed gels over a temperature range of 27–32°C. The gelling temperature decreased with increasing xyloglucan concentration. In vitro release profiles for indomethacin and diltiazem were characterized as a square-root of time function with diffusion coefficients increasing with temperature increases from 10 to 37°C. The slower in vitro indomethacin release from gels was confirmed in vivo where broader absorption peaks and longer residence times were noted. There were, however, no significant differences in bioavailability between the thermal gelling formulations and conventional indomethacin suppositories.

Ryu et al. (2) examined mucoadhesive liquid suppositories that combined bioadhesive properties with thermal gelling polymers. Hydroxypropylcellulose, polyvinylpyrrolidone, carbopol, polycarbophil and sodium alginate were used as bioadhesive polymers in thermal gelling polymers comprised of poloxamer 407 and poloxamer 188. Gellation temperatures between 30 and 36°C were obtained with mucoadhesive forces ranging from 430 to 5800 dyne/cm^2. With propranolol as a model compound, bioavailability increased as the mucoadhesive force increased and dosage form migration distance decreased. There was, however, no direct relationship between bioavailability and gellation temperature. Sodium alginate and polycarbophil afforded the greatest mucoadhesive forces and most significant improvements in propranolol bioavailability. Sodium alginate was also free of any quantifiable adverse effects on rectal tissue. The studies suggest that reduced formulation migration as a function of mucoadhesive potential was the primary causative factor for the improved bioavailability of propranolol.

Watanabe et al. (4) have reported improved rectal absorption with reduced mucosal irritation utilizing rectal gels comprising water-soluble dietary fibers, xanthan gum and locust bean gum. Absorption of buprenorphine was more rapid than that observed from polyethylene gels with comparable extents of bioavailability. Mean residence times increased with increasing gum concentrations. Most importantly, the degree of mucosal irritation from these dietary fiber gels was significantly less than that observed with polyethylene based suppositories.

Controlled-release formulations

Controlled-release formulations are designed to release the active agent in a sustained and controlled fashion. They have been the subject of considerable research but have yet to make a significant impact. Hydrogels have been shown in human clinical studies to provide an acceptable polymeric system for rate-controlled delivery of antipyrine and theophylline (6). Rate-controlled osmotic delivery systems have also proven useful in clinical studies in effecting systemic drug delivery comparable to that of intravenous administration for well absorbed drugs (7). Since the total acceptable size of a rectal formulation significantly exceeds the size possible for oral formulations, rectal administration for the purposes of controlled-release offers a significant advantage. A major limiting factor is, however, the need to incorporate controlling agents designed to regulate drug release which would significantly increase the total size of the dosage form. Since adult rectal dosage forms are acceptable up to 2.5 g, the total drug load which can be formulated in a rectal controlled-release formulation can be 2–3 times that possible in an oral formulation. For some therapeutic agents, this higher drug load can offer an advantage which

is not achievable via the oral route. Development and marketing of rectal controlled-release formulations will, however, still be disadvantaged because of the perceived reluctance of patients to employ this route and problems of poor patient compliance.

Marketed drugs and therapeutic classes

Only a limited number of therapeutic agents are currently marketed in the United States as rectal dosage forms. A survey of the 1994 American Hospital Formulary Service shows that 19 agents are sold for systemic therapeutic indications (Table 2) and 15 agents for local GI applications (Table 3), including imaging agents for diagnostic purposes. Many products for local GI application are over-the-counter (OTC) products for treatment of local inflammatory reactions and hemorrhoids. As is readily evident from the limited number of therapeutic agents available for rectal administration, this dosing route does not represent a major share of the physician's choices for drug therapy.

Worldwide market

In certain areas of the world, particularly some European countries and Japan, rectal dosage forms are somewhat more accepted by the patient population and, hence, development of rectal dosage forms has surpassed that in the United States. According to a survey in 1970, approximately 7.5% of all prescriptions in France were formulations intended for rectal administration (8). Even though a few countries may find rectal dosage forms more acceptable, these still represent a small area of the world-wide market share which can be assigned to rectal drug therapy.

Table 2 Rectal dosage forms marketed in the United States for systemic indications

Therapeutic category and drug	Drug load, solid[a] (mg)
Antihistamine	
Promethazine	12.5–50
Antimigraine	
Ergotamine	2
NSAID	
Aspirin	60–1200
Indomethacin	50
Analgesic	
Hydromorphone	3
Morphine	5–30
Opium	30–60
Oxymorphone	5
Acetaminophen	120–650
Insomnia	
Pentobarbital	30–200
Chloral hydrate	325–650
Promethazine	12.5–50
Tranquilizer	
Chlorpromazine	25–100
Prochlorperazine	2.5–25
Bronchodilator	
Aminophylline	105
Antiemetic	
Thiethylperazine	10
Trimethobenzamide	100–200
Hyperkalemia	
Polystyrene sulfonate	1250[b]
Portal-systemic encephalopathy	
Lactulose	Variable[c]

[a]Unless otherwise indicated.
[b]Suspension.
[c]Solution.
(From McEvoy, GK., Ed. *American Hospital Formulary Service;* American Society of Hospital Pharmacists, Inc.: Bethesda, MD, 1994.)

PHYSIOLOGIC AND PHARMACEUTICAL ISSUES RELEVANT TO RECTAL DRUG DELIVERY

Physiology and Biochemistry of Rectal Tissues

Anatomical considerations

Unlike the small intestine and upper colon, the vasculature draining the rectal cavity does not totally direct the blood supply to the liver (9). The lower and middle hemorrhoidal veins of the rectum bypass, at least partially, the portal circulation during their first pass into the general circulation, allowing absorbed drug to exert systemic effects prior to possible metabolism and excretion via hepatic mechanisms. Lignocaine, propranolol, and salicylamide have been shown in clinical studies to attain greater systemic bioavailability when administered rectally than when given orally (10). The rectal cavity is also drained by extensive lymphatic circulation which facilitates absorption and systemic exposure of absorbed drugs (11).

Although extensive villi and microvilli are not present in the rectum and colon tissue, sufficient surface area is present to allow absorption of readily permeable drugs. The lack of motility in the rectum and colon, as opposed to extensive motility in the small intestine, provides an additional advantage in terms of maintaining maximum concentration gradients at the absorptive surface. Together with a limited fluid volume in the lower colon, typically 2–3 ml of inert mucous fluid in the absence of fecal material, the static environment of the rectum and lower colon provides an area for maintaining significantly higher

Table 3 Rectal dosage forms marketed in the United States for gastrointestinal indications

Therapeutic category and drug	Drug load	Physical form
Laxatives		
Senna	30 mg	Solid
Glycerin	4 ml	Solid or liquid
Mineral oil	—	Liquid
Potassium bitartrate		Solid
Dibasic sodium phosphate	—	Solution
Docusate sodium	—	Suspension
Hemorrhoids		
Hydrocortisone	100 mg	Suspension or cream
Hydrocortisone acetate or butyrate	—	Aerosol, foam, and suspension
Dibucaine	—	Ointment
Proxamine	1%	Ointment
Proctitis, colitis		
Belladona	16.2 mg	Solid
Mesalamine	500 mg	Solid
Enteropathogenic diarrhea		
Neomycin	—	Retention enema
Contrast imaging agents		
Barium sulfate	5–70% (w/w)	Suspension
Diatrizoate	60–66%	Solution

(From McEvoy, G.K. Ed., *American Hospital Formulary Service;* American Society of Hospital Pharmacists, Inc.: Bethesda, MD, 1994.)

drug concentrations than is readily achievable in the small intestine. On the negative side regarding potential for drug absorption, the intercellular junctional complexes are tighter in colon and rectum than in small intestine (12) which may reduce opportunities for small, water-soluble drugs to permeate intercellular spaces and gain access to the systemic circulation without passing through cellular membranes.

Biochemistry

Cellular metabolism of drugs, as they pass through the mucosal barrier of the rectum or colon, can be expected to be similar to that seen in the small intestine since the basic intracellular metabolic machinery is common to epithelial cells. The major difference relative to drug metabolism occurs in the enzymes to which drugs are exposed in the intestinal lumen and on the apical membranes of the epithelial cell layer. Since the colon and rectum do not serve digestive functions, the lumenal enzymes, which are actively secreted in the upper small intestine, are not present to any significant extent. As such, proteolytically labile drugs such as peptides and proteins should exhibit greater stability if released in the rectum or lower colon. Saffran et al. have shown that vasopressin, a peptide subject to proteolytic hydrolysis, is more active when administered by the rectal route than by oral administration (13). Significant rectal absorption of growth hormone (14) and insulin (15) have also been demonstrated with the help of absorption enhancing agents. The apical membranes of the small intestine epithelial cell layer express high levels of membrane-associated or membrane-bound enzymes, such as peptidases and saccharidases, which are not present in high amounts on the apical surfaces of epithelial cells in the rectal cavity. This absence of membrane surface metabolic potential affords advantages when delivering drugs susceptible to enzymatic degradation. These membrane-associated enzymes are, however, linked to direct transport carriers for specific nutrients, notably amino acids and sugars. Carriers for many of the vitamins are also present in small intestinal tissue. The relative absence of these transport mechanisms in colon and rectal tissue (16) eliminates this mechanism of absorption as a viable route for rectal drug delivery. Since most of these amino acid, saccharide, and vitamin carriers have relatively specific structure and transport requirements, the absence of these systems in colon or rectal tissue affects only drug candidates with significant structural similarity to natural substrates.

The pH of the rectal compartment is essentially neutral, ranging from 7 to 8, with minimal buffering capacity as compared to the small intestinal milieu. Suppositories or solutions formulated to maintain a specific pH in order to

optimize drug absorption typically will function at that pH following administration. This can be a significant advantage with drugs whose permeation properties are optimized near neutrality. It should be kept in mind, however, that the controlling pH at the epithelial membrane surface, which is under the overlying mucous layer, is still in the range of pH 6.0–6.5 as it is throughout the small and large intestine. Therefore, even though lumenal pH may favor drug absorption and diffusion from the lumen to the cell barrier, the effective pH at the cellular barrier is not drastically different from other regions of the intestinal tract. In this sense, perceived pH advantages of rectal drug administration may be obviated by the basic surface pH which is characteristic of mucosal tissue.

Model Systems and Techniques

Whole animal models

Preliminary in vivo evaluation of the rectal absorption potential of drug candidates is most easily achieved in a rat model (17, 18). Animals can be maintained at surgical plane anesthesia for 120–180 min, and drug solutions or suspensions can be directly instilled into the rectal cavity. Utilizing a slight elevation above horizontal, instillation of approximately 0.25 ml is readily achieved in rats without loss of fluid from the rectal compartment. Purse-string sutures or moderate pressure clamps can also be used to prevent leakage of administered solutions from the rectal cavity. In most cases, it is advisable to fast animals for 12–16 h prior to study to void the colon and rectal cavity of fecal material which may interfere with administration of the solution or absorption of the drug itself. Microsuppositories can also be evaluated in the rat model by utilizing specially designed molds to prepare small dosage forms, but care must be taken to guarantee drug content uniformity in these small devices. Additionally, since drug absorption can be influenced by the choice of suppository base, this must be taken into consideration in any analysis of the rectal absorption potential of a drug candidate.

Rabbits have been another common animal model utilized for examining rectal drug absorption. Constraints with using this animal model are similar to those encountered with the rat model, although there is more latitude concerning the volume (solid or liquid) of the dosage form which can be tested. A possible drawback to the rabbit model is evidence suggesting that the rabbit colon is somewhat more "leaky" than the colon in other species. In this regard, the rabbit model may overestimate the extent of drug absorption achievable for small, water-soluble compounds which utilize intercellular transport pathways via water flux.

For evaluation of dosage forms designed and formulated for human use, the Beagle dog presents an ideal animal model (18, 19). Solid suppositories (up to 2.5 g total weight) or microenemas (up to 5 ml volume) can be readily tested in Beagles without concern for loss of dosing vehicle from the rectal compartment. Since the physical dimensions of the dog rectum approximates those of the human rectum, variables such as spreading of suppository bases can be reasonably well evaluated. The dog is obviously a convenient model for blood sampling and pharmacokinetics and is, therefore, well suited for the evaluation of rectal dosage forms. Studies from the author's laboratories and others have shown that dosage-form performance criteria generated in Beagle dog models are accurate predictors of performance in human clinical trials (20).

In vitro models

For assessing the absorption potential of specific drug candidates or conducting studies evaluating correlations between drug structure and transport, in vitro models may provide the best approach. Both the tissue-diffusion cell systems and cultured colon cell lines have proved to be particularly useful.

Numerous investigators have employed diffusion chambers of various designs (e.g., Ussing chambers, Sweetana–Grass diffusion cells) to evaluate the permeation properties of drug candidates (21, 22). These systems offer a distinct advantage that drug solutions may be added to the donor compartment under a variety of conditions (e.g., varying concentrations, pH, excipients). Samples are withdrawn periodically from a receiver compartment and analyzed for drug and metabolite content to obtain a true measure of permeation across the cellular barrier. In establishing procedures for these diffusion cell studies, the underlying muscle layer can be teased away and only the intact mucosal cell layer mounted in the diffusion chamber. Since the underlying muscle layer is not a barrier encountered under normal physiologic conditions, this method more accurately reflects the true cellular barrier to drug transport. In should be noted that, in many cases, any mucus layer normally overlying the mucosal cell layer may be disrupted and removed by the physical manipulations and tissue washing procedures normally employed in the experimental design. Therefore, for drugs where diffusion through the mucus layer may represent the rate-limiting step, this model may overestimate drug permeation unless great care is taken to maintain the mucus layer. Conversely, the use of mucolytic agents can be employed to ensure a mucus-free cell layer if true cellular drug permeability is to be determined. Work in the author's laboratories has demonstrated that the Sweetana–Grass diffusion cell model with muscle-free mucosal layers is

reasonably resistant to experimental conditions. The pH can be varied between 5 and 8 without significant damage to the mucosal layer. Additionally, excipients such as DMSO or ethanol, can be utilized up to 10% (v/v) in order to improve solubility of drugs whose absorption may be limited by poor aqueous solubility. Finally, our experiments have shown that muscle-free mucosal strips can be maintained with good viability for up to 120 min at 37°C, although this should be experimentally determined in each laboratory using this model to ensure that tissue damage is not affecting the measured drug transport values. Typically, standard metabolic viability assays and microscopy are suitable for confirming tissue viability.

Another in vitro model that has experienced significant growth in utilization in drug transport studies and which may provide useful information relative to rectal or colonic drug absorption is cultured cell monolayers. HT-29 and Caco-2 cells are two cell lines commonly employed for such studies (20, 25). Both are human colon-cancer cell lines which can be grown on membrane filters and readily form confluent monolayers with intact tight junctional complexes (typically $>250\ \Omega\ cm^2$. They can be used in experimental designs similar to the diffusion cell models. These cells are non-mucus secreting cell populations which resemble fetal small intestine in many of their metabolic properties. Although these models are useful for quantifying drug transport across colon cell lines, certain limitations must be kept in mind. First, aqueous pathways in these confluent monolayers are significantly reduced compared to the in vivo situation. In other words, the intercellular pathway, as monitored by electrical resistance, is less "leaky" than that encountered in normal colon or rectal tissue and drug transport studies may underestimate the absorption of drugs which utilize the paracellular pathway. Second, there is evidence to suggest that some of the carrier systems present in small intestinal epithelial cells (e.g., vitamins, dipeptides) are also present to some extent in these cell lines (26, 27) which may provide misleading information on the rectal absorption potential for compounds which that utilize these carriers. Finally, these are transformed cells which may or may not present metabolic barriers comparable to that seen in normal colon or rectal tissue. Care must be taken in interpreting data from transport studies which show parent drug metabolism during the absorptive phase since this may or may not also occur in vivo.

Advantages over Oral Systems

Improved enzymatic drug stability

It is well known that the oral delivery of many drugs, particularly peptides and proteins, is limited due to poor absorption and/or stability in the stomach and upper intestinal tract. Many proteolytic and other enzymes in the stomach and small intestine result in drug degradation which prevents effective absorption following oral administration. As discussed above, degradative enzymes are present to a much lesser degree in the rectum and therefore many drugs that cannot be administered effectively orally can be administered rectally without as much enzymatically catalyzed degradation. Examples include vasopressin (13), growth hormone (14), and insulin (15). It has been found necessary to include absorption enhancing agents for growth hormone and insulin.

Partial avoidance of hepatic first pass

The rectum is extensively supplied with blood from the various rectal arteries. It is drained by at least three veins (28) and drug absorption primarily occurs through this venous network. Although there is substantial intermingling of these veins due to several anastomoses, it is usually reported that the inferior and middle rectal veins drain into the inferior vena cava. This allows drugs absorbed by this route to partially bypass the portal system and the associated first-pass metabolism in the liver. As an example of this effect, de Boer and Breimer (10) have shown that the systemic bioavailability in humans for lignocaine is about twice that observed following oral administration. It has been suggested that about half of rectally administered drug avoids hepatic presystemic metabolism. Clinical studies have also shown higher systemic bioavailabilities for propranolol and salicylamide when administered rectally compared with oral administration (10). Studies in rats suggest that first pass metabolism is almost totally avoided by rectal administration. For example, the bioavailability of nitroglycerin in rats following unrestricted rectal instillation was about 27% compared to 2% from oral dosing. When the length of rectal tissue exposed to the drug was restricted to 2 cm from the anus, the bioavailability increased to about 90% (29).

The fact that rectal administration in humans only partially avoids delivery of the drug to the portal system has been suggested as an advantage of rectal administration of insulin over parenteral administration (30). Delivery of insulin to the portal blood system is suggested to be more physiological than delivery to the peripheral cells from subcutaneous injections.

Higher drug load

In general, oral administration in a single tablet is limited to about 1 g. Typically, suppositories intended for adults can be as large as 2.5 g. This should allow for two to three

times higher drug loads to be administered, depending on the amounts of other excipients necessary in the formulation of the suppository.

Lymphatic delivery

Some studies have indicated that significant amounts of some drugs are transported through the lymphatic systems following rectal administration. For example, Caldwell et al. (11) have examined the importance of lymphatic transport of water-soluble drugs following rectal administration in the presence of salicylate-type adsorption enhancers. They observed that following i.v. injection to the rat, the concentration of phenol red in the plasma and the lymph (collected from the thoracic duct) were similar. They further found that concentration of phenol red in the lymph after rectal administration to rats via cannulated thoracic ducts was more than 100 times greater than corresponding plasma concentrations when 5-methoxysalicylate was used as an adjuvant. Rectal administration of phenol red in the presence of 5-methoxysalicylate to rats with intact thoracic ducts produced plasma levels of phenol red which were about fivefold greater than those found in the rats in which lymphatic drainage had been diverted. As shown in Fig. 1, insulin was also transported primarily through the lymphatic system to the general circulation. However, theophylline exhibited much lower lymphatic transport.

Constant and static environment

Compared to the oral route of administration, the rectal route provides a much more constant environment for the drug as it is absorbed. An orally administered drug must usually pass through a series of diverse environments prior to absorption. This includes transit through the stomach and the small intestine and perhaps to the large intestine and colon, depending on the drug and the absorption site. The pH and absorptive sites in the GI tract change significantly as the drug traverses it. This can lead to a more complicated set of conditions which influence absorption compared to the rectum which is a short part of the GI tract with relatively constant absorption characteristics.

Patients with swallowing difficulty

For a number of patients, especially children and elderly, problems associated with swallowing and nausea when taking oral medication can be largely obviated by rectal administration. Patients with gastrointestinal disorders or after surgery often have difficulties taking drugs by mouth. Rectal administration may be a good alternative to oral administration in these types of situations.

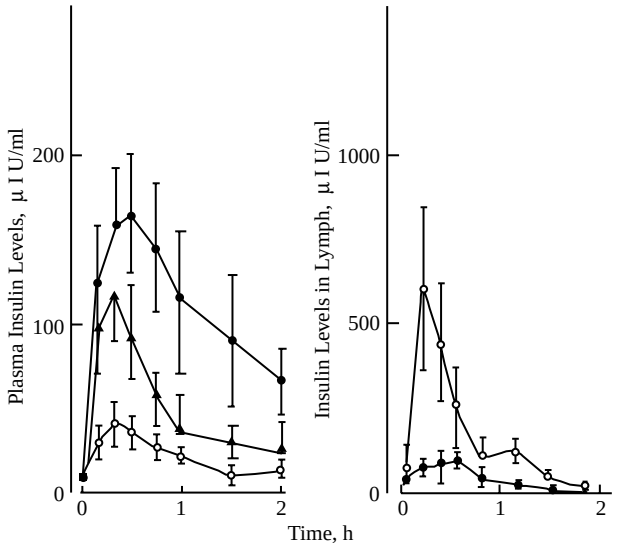

Fig. 1 Concentration of insulin in the plasma and lymph of rats following intramuscular administration of 0.8 IU/body insulin (●), rectal administration of 2.0 IU/body insulin in the presence of 10 mg/body 5-methoxysalicylate and intact thoracic duct (▲), and rectal administration of 2.0 IU/body insulin in the presence of 10 mg/body 5-methoxysalicylate with the thoracic duct cannulated for collection of lymph (○). The error bars represent standard deviations with $n = 6$. (From Ref. 11.)

Avoidance of overdosing

For some patients and with certain drugs, such as certain sedatives, oral administration may raise a concern with respect to the possibility of severe accidental or intentional overdosing. This danger is practically eliminated by rectal administration. Whereas it is relatively easy for a patient to swallow a number of tablets, it is much more difficult to administer numerous suppositories rectally at the same time. Thus rectal administration may be indicated for patients for whom overdosing is a significant concern.

Disadvantages Compared to Oral Systems

Patient acceptance and compliance

In some cultures, such as in the United States, there is a reluctance by many to consider rectal administration. This has resulted in a tendency by pharmaceutical marketing groups to avoid rectal dosage forms, except for the most obvious indications and situations where other dosage forms have substantial disadvantages. Frequently, it is inconvenient to receive or administer a suppository or other rectal dosage form, thereby reducing patient compliance. Thus, the need must be great in most cases for rectal administration to be seriously considered.

Potential for nonspecific drug loss

There are at least two common problems that can lead to drug loss following rectal administration. First, for effective absorption, the dosage form must be retained in the rectum. Thus if the dosage form or parts thereof are lost prematurely from the rectum, drug absorption will be substantially reduced. A study with children showed that when thiopentone suppositories were voided within 40 min, an effective plasma level was maintained for less than 2 h, whereas when the suppositories were retained, an effective level was maintained for about 24 h.

Second, there is the possibility that the drug or some important excipients may interact with constituents of fecal matter or material fluid present in the rectum. This may reduce the drug absorption and diminish effectiveness.

Limited fluid in the rectum

The amount of liquid in the rectum has been reported to be about 3 ml. This is small compared to the volume of fluid available throughout the GI tract when a drug is administered orally. Such a small volume of fluid can limit dissolution of drugs, particularly those with low aqueous solubility. It also may be a constraint to the rapid dissolution and release of compounds from water-soluble vehicles where dissolution of the vehicle is considered to be the rate-determining step in drug release from the vehicle.

Formulation

There are a number of formulation variables and considerations that can lead to difficulties in rectal drug absorption, including the melting and liquefaction characteristics of the vehicle. The solubility of the drug in the vehicle, the particle size of the drug, the vehicle spreading capacity, the viscosity of vehicle and excipients at rectal temperature, and possible retention of the drug by excipients, all can affect the rate of release and consequent drug absorption. Furthermore, the pK_a of the drug, the pH of the rectal fluids, the presence of buffers, and the buffer capacity of the rectal fluid as well as the partition coefficient of the drug influence drug absorption and must be considered in the formulation of a suppository or other rectal dosage form. Storage temperature, time, and conditions can have a profound effect on both the stability and release characteristics of a drug from a rectal dosage form. Each of these considerations lead to potential difficulties in the formulation, manufacture and distribution of rectal dosage forms.

Expense

Suppositories and other rectal dosage forms are more expensive to prepare and dispense than simple tablets. Therefore, unless there is a significant need and advantage by utilizing a rectal dosage form, suppositories are not likely to be used. Recently, techniques have been developed to prepare suppositories more efficiently which could lead to lower manufacturing costs.

Drug Classes Useful for Rectal Administration

Drugs that are currently marketed in the United States for rectal delivery are shown in Tables 2 and 3. In addition to drugs intended for local effects, many other types can be administered rectally for systemic activity, such as drugs with high hepatic first-pass extraction, drugs for which lymphatic absorption is important, and compounds requiring a relatively high therapeutic dose. Generally, drugs requiring significantly more than 500 mg per tablet are not easily taken orally and in some cases may be candidates for rectal delivery.

Although products are not currently marketed containing proteins and peptides, the literature contains several examples of rectal absorption of peptides and proteins. Typically proteins and peptides require some type of penetration-enhancing adjuvant in the formulation to facilitate absorption. Examples of peptides and proteins that have shown significant rectal absorption include: insulin, lysozyme, calcitonin analogs, phenylalanine and di-, tri-, and tetraphenylalanine, as well as gastrin, pentagastrin and tetragastrin (31).

ABSORPTION CHARACTERISTICS AND REGULATION OF DRUG ABSORPTION

Control or Modification of Rectal Drug Absorption

pH partition

The mechanism for absorption from the rectum appears to be similar to that observed for the rest of the GI tract, that is, passive diffusion. Drugs are best absorbed through the rectal mucosa in their un-ionized or neutral form. Drugs with high partition coefficients (more lipophilic) tend to be better absorbed. There are, however, conflicting reports in the literature with some suggesting that simultaneous absorption of ionic species is possible. That is particularly true for relatively small molecules. If the drug can exist in the unionized state at physiological pH, other factors being equal, absorption is improved.

Solubility

As was pointed out earlier, the volume of fluid in the rectum is very small. In most cases, it is believed that the drug should be dissolved in the rectal fluid prior to absorption. This requires that drugs have a reasonably high solubility to be efficiently absorbed from the rectum. Voigt and Falk (32) reported a direct relationship between water solubility and release rate for 35 different compounds. Generally, when a compound can be presented in relatively low solubility form (e.g., neutral acid) or as a more water-soluble form (e.g.,the sodium salt), the higher the solubility and consequently the higher the dissolution rate in the rectal fluid, the better is absorption. This factor has to be balanced with the fact that an unionized species tends to pass through the rectal mucosa more readily.

Drug solubility also affects the choice of suppository base or other vehicle. Generally, the drug should have little tendency to remain in the vehicle upon melting or dissolution. Therefore, it is usually suggested that water soluble drugs are best delivered from fatty vehicles and that more lipophilic compounds from water-soluble vehicles.

Molecular size

The smaller the drug molecule, the more readily it can be absorbed. For larger molecules, some type of facilitated transport or the use of penetration enhancers have been found to increase drug absorption from the rectum as well as from other delivery routes.

Charge

Charged molecules have been found to pass through the rectal mucosa less effectively than neutral molecules in most cases. This can sometimes be overcome by modifying the pH or allowing the charged species to interact with another molecule or ion that helps neutralize the charge. Ion pairs, for example, hold some promise for overcoming the drawbacks of charged species. From a solubility point of view, charged species are generally preferred. Often a balance between high solubility and penetration through the rectal mucosa must be obtained, requiring some compromise in properties of choice. It has often been observed that in vivo differences are often less pronounced than in vitro differences. Furthermore, penetration enhancing agents can often improve the delivery of relatively large water-soluble drugs.

Nonspecific adsorption

The surface properties of a solid may significantly affect the drug when it reaches the interface between the vehicle and the rectal fluid. The amount of wetting, as demonstrated by contact angle, that occurs or changes in the interfacial tension as caused by interactions with surface-active agents in the vehicle or rectal fluid may have a profound effect on dissolution and consequent absorption of the drug. This can often increase the availability of the drug. On the other hand, adsorption or complex formation with surface-active agents may reduce the availability of the drug and its absorption.

Spreading of the administered formulation

For optimal drug absorption, it is important that the suppository or vehicle melts or dissolves rapidly and spreads over the rectum walls. Thus the rheological behavior of the vehicle can have a significant effect on the release of the drug and the ability of the drug to come into contact with the rectal mucosa. Several studies have suggested that the viscosity of the vehicle is very important for the release of the drug from the vehicle. Studies that compare the spreading behavior of suppository bases and their hydrophilic-lipophihc balance (HLB) values have been inconclusive. Although spreading directly determines the area from which release from the vehicle can occur and thus absorption, there is also the potential difficulty that concentration and thermodynamic activity of the drug may be reduced if it is allowed to spread too much and particularly too high up the rectum. This may result in absorption by the upper hemorrhoidal vein and into the portal blood supply with increased first-pass metabolism.

Yahagi et al. (3) have reported improvements in lidocaine bioavailability utlizing a unique double phase suppository that minimizes spreading of an administered suppository. The front or anchoring phase of the suppository contains Witepsol-H15, Carbopol, 934P, and wax. The terminal layer or drug releasing layer contains Witepsol-H15, Carbopol 934P, and lidocaine. Carbopol provides the bioadhesive properties and the wax confers physical strength to the suppository formulation. This formulation provided greatly prolonged plasma lidocaine levels with improved bioavailability. The authors suggest that a combination of improved rectal retention (decreased formulation migration due to bioadhesive nature) combined with a somewhat slower drug release rate maximizes avoidance of absorption into vascular pathways subject to first-pass hepatic metabolism. This approach may prove useful for drug candidates subject to high first pass effects.

Optimizing Drug Absorption

Enhancing agents

Over the past 20 years, a variety of agents have been identified which significantly increase the permeability of

the GI tract to drug absorption. The enhancing action of a variety of absorption-promoting adjuvants on rectal absorption has been extensively discussed (33). Included are acylcarnitines (19), acylcholines (19), salicylates (34), bile salts (35), phenothiazine derivatives (36), enamines (37), and fatty acids (38). Strong chelating agents and phenothiazines appear to enhance the rectal absorption of both low and high molecular weight compounds with a constant ratio of absorption via a paracellular route. Diethylmaleate enhances rectal absorption of low molecular weight compounds via a transcellular route. Various salicylates, diethyl ethylene malonate, and various fatty acids have been found to enhance both the paracellular and transcellular routes of absorption (33). In some respects, rectal drug administration is optimally suited for coadministration of drug entities with absorption-enhancing agents.

Work in the authors' laboratories has clearly shown that the presentation profile of drug and enhancing agent is critical to optimal activity (19). With agents like the acylcarnitines and acylcholines, the effective increase in permeability due to absorption enhancement is transient with nearly complete loss of activity approximately 30–60 min after dosing. In order to take advantage of the narrow time window of increased permeability, it is essential that the drug and enhancing agent be present at the mucosal barrier at the same time and in sufficient concentration to effect the permeability change. The low motility and limited fluid content of the rectal compartment is ideal for optimizing these requirements. When administered orally, enhancing agents are routinely less effective than when given rectally, presumably due to motility and dilution of the drug and enhancer. The necessary temporal and spatial dosing of a drug and enhancer can be achieved more readily via the rectal than the oral route. Design and performance determination of solid rectal suppositories must, however, address the release profiles of both agents which adds to the complexity of the formulation process. This can be achieved, as demonstrated in a previous study, with sodium cefoxitin and salicylate-type enhancing agents (20). In this study, a rectal suppository of the antibiotic with enhancing agent was shown to be essentially bioequivalent to an intramuscular injection of the antibiotic alone. The rectal absorption of proteins can also be enhanced by salicylates, as shown for insulin in Fig. 2. As an alternative to injectable administration, a rectal suppository offers definite advantages in terms of patient compliance and out-of-clinic administration.

pH control

As discussed earlier, the pH of the rectal fluid can have a marked effect on the absorption of drugs from the rectum. Since the rectal fluid has a relatively low buffering capacity and the volume of the rectal fluid is small, it might be expected that the contents of the rectal dosage form largely control the pH of the rectum during administration. On this basis, one may be able to utilize the pH characteristics of the drug and incorporate suitable buffers and other excipients in the dosage form to control the pH. It has been reported (40) that a solution having a buffer capacity of 0.1 was sufficient to maintain a pH at about 5.9 during perfusion in humans. In this study, the pH was restored to normal at a rate of about one half a pH unit per minute, following removal of the perfusate. The body appears to try to maintain the pH at the absorbing surface relatively constant by secretion but often requires some time to be able to return to the normal pH after administration of a rectal dosage form having significant buffer capacity and differing pH.

Solubilizing agents

It would be expected that solubilizing agents may increase the rate of drug release from a suppository base by increasing the dissolution rate and perhaps by modifying the viscosity and interfacial tension of the vehicle with the rectal fluid. In addition to the effect that a solubilizing agent or a surfactant can have on the drug and the vehicle, the surfactant may also have an effect on the mucous coating of the rectal membrane. This may increase absorption by reducing the thickness of the layer through which the drug must traverse or it may act as a penetration enhancer by increasing the permeability of the membrane through damaging the rectal mucosa. Nishihata et al. (39) reported that sodium lauryl sulfate appears to interact with the lipoidal fraction of the rectal membrane with irreversible effects in the short term. It was further reported (41) that various metabolic inhibitors had little, if any, effect on the enhancement observed with the surfactant polyoxyethylene 23-lauryl ether. However, definitive studies have not been reported which clearly delineate the complexities that can occur from the simultaneous involvement of several factors that influence drug absorption from the rectum. It has been suggested that for an oleaginous base, solubilization, particularly with a decrease in vehicle viscosity, should improve rectal drug delivery.

Viscosity modifiers

The luminal pressure of the rectal mucosa can act as a shearing stress and influence the rheological behavior of substances showing either plastic or psuedoplastic behavior. It is possible that the viscosity at the shearing stress supplied by the rectum is more important than the yield value of the suppository. It appears that viscosity is very important for drug release from suppositories where

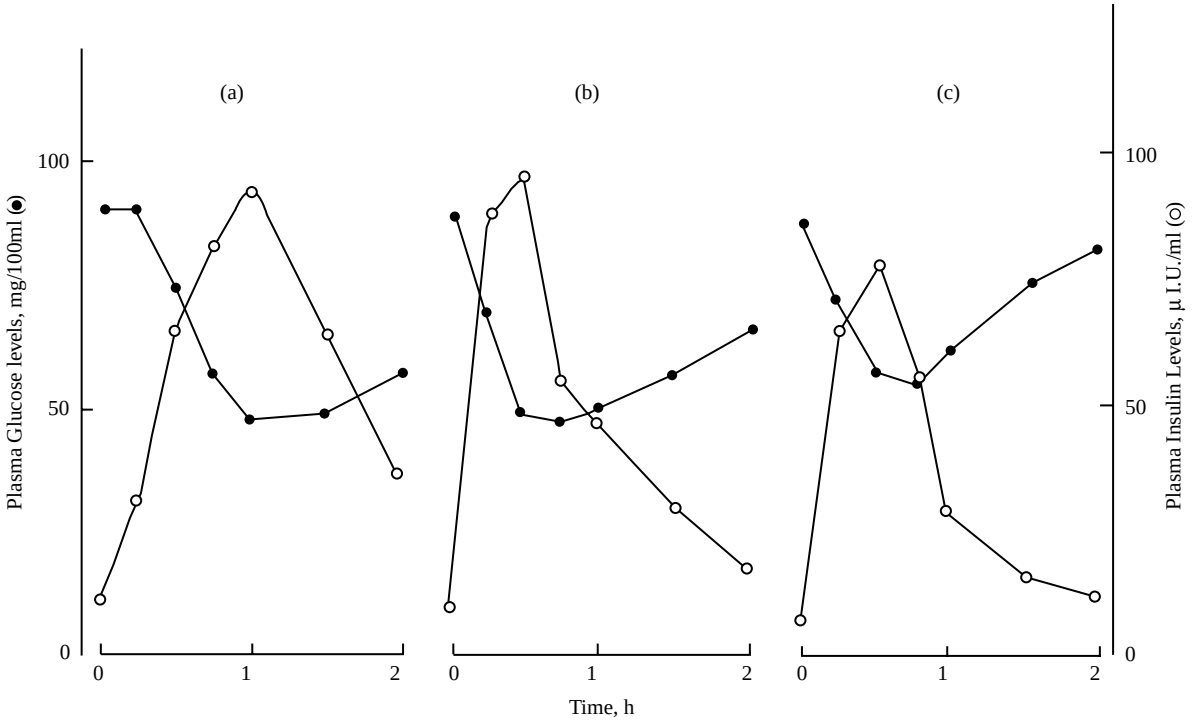

Fig. 2 (a) Concentrations of glucose (mg/100 ml) and insulin (μ IU/ml) in the plasma of dogs following an intramuscular injection of 10 IU of insulin. (b) Concentrations of glucose and insulin in the plasma of dogs after the administration of a 0.5 ml microenema containing 20 IU of insulin with 150 mg of sodium 5-methoxysalicylate in a 0.9% NaCl solution containing 4% gelatin. (c) Concentrations of glucose and insulin in the plasma of dogs following a 0.5 ml microenema containing 20 IU of insulin with 300 mg of sodium salicylate in a 0.9% NaCl solution containing 4% gelatin. (From Ref. 39.)

the melted material behaves like a Newtonian fluid. Generally, the lower the viscosity, the quicker and more complete the release of the drug from the vehicle and the higher the absorption of the drug.

FUTURE OF RECTAL DRUG DELIVERY

Market Potential

Even under the best of conditions and therapeutic needs, rectal dosage forms will remain only an alternative to oral administration. Due to problems associated with patient acceptance and compliance, the need to refrigerate many suppository bases, and the inconvenience of dosing, it is extremely unlikely that rectal drug administration will ever play a significant role in the pharmaceutical market. However, in specific fields of the therapeutic regimen, rectal dosage forms can have a significant impact and can address the needs of several patient populations that are poorly fulfilled by conventional oral formulations.

Examples Where Oral Administration Does Not Satisfy Therapeutic Needs

For certain groups of the patient population, oral dosing is either not desirable or impossible. Several antibiotics which are administered postoperatively via parenteral routes are not available as oral formulations because of the nature of the drug or its absorption limitations, or they are unacceptable due to swallowing difficulties in this patient subset. In these cases, rectal formulations that can contain a significantly higher drug content than oral formulations and which can be administered without difficulty to hospitalized patients, offer an attractive alternative and can be utilized to wean patients from parenteral to non-parenteral drug delivery. Rectal formulations of medications for pain control and sedation fit within this postoperative category.

Both children and the elderly experience swallowing problems with oral formulations. A limited market already exists in pediatric therapeutics which addresses this problem. Although development of rectal formulations for the elderly has not been addressed extensively, with the expanding number of patients in this age group, the need

for acceptable alternatives to oral dosing may increase efforts to develop rectal formulations.

As indicated previously, two general classes of drugs may be most amenable to formulation in rectal dosage forms. Drugs which require relatively high dosing, such as many of the antibiotics, are good candidates for rectal formulations which minimize the need for multiple oral dosings in order to reach the desired drug levels. Drugs that are substrates for proteolytic activity in the upper GI tract, particularly peptides and proteins, may find a useful application in rectal dosage forms if their absorption profile can be improved. Finally, in some very specific cases where extensive first-pass metabolism limits a drug's usefulness, rectal formulations may provide an attractive alternative.

SUMMARY

Rectal administration of therapeutic agents represents a narrow part of the total pharmaceutical approach to disease management but it holds promise for increasing applications. Although rectal administration will not become the first line of drug delivery, the increasing pressure to find exploitable delivery routes for peptides and proteins may well find some answers in rectal administration. From a drug stability perspective, the low level of proteolytic activity in the colon and rectum offers hope that active agents can be delivered to the cellular membrane in effective concentrations. Assuming that techniques can be developed to increase the permeability of the GI tissue to these agents, rectal administration may become a more widely employed route of delivery.

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